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ORIGINAL PAPER

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Suicide attempters: biological stressmarkers and adverse life events

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Abstract Risk factors for suicidal behaviour include adverse life events as well as biochemical parameters acting, e.g. within the hypothalamic–pituitary–adrenal axis and/or monoaminergic systems. The aim of the present investigation was to study stressful life events and biological stress markers among former psychiatric inpatients, who were followed up 12 years after an index suicide attempt. At the time of the index suicide attempt, and before treatment, cerebrospinal fluid (CSF) samples were taken, and 24 h (h) urine (U) was collected. 3-Methoxy-4-hydroxyphenylglycole (MHPG) in CSF and 24 h urinary samples of cortisol and noradrenaline/adrenaline (NA/A) were analysed. Data concerning stressful life events were collected retrospectively from all participants in the study through semi-structured interviews at follow-up. We found that patients who reported sexual abuse during childhood and adolescence had significantly higher levels of CSF-MHPG and U-NA/A, than those who had not. Low 24 h U-cortisol was associated with feelings of neglect during childhood and adolescence. In conclusion, this study has shown significant and discrepant biological stress-system findings in relation to some adverse life events.

Key words suicide attempt · catecholaminergic markers · U-cortisol · adverse life events

Introduction

A suicide attempt is regarded as a strong risk factor for a future suicide attempt or actual suicide. Other variables, i.e. depression, alcohol and drug abuse as well as some biological markers and severe life events are known to be of importance for suicidal behaviour [22].

There might be an interplay between underlying biological factors and psychosocial factors leading to suicidal behaviour in vulnerable patients with psychiatric disorders. The biological vulnerability is probably reflected by genetic factors and abnormalities that involve the serotonergic system [11, 24, 35] as well as the stress-system [40]. Mann [23] suggested a stress-diathesis model for suicidal behaviour, which involved the hypothalamic–pituitary–adrenal (HPA) axis and the noradrenergic system as well as a vulnerability shown as a decreased serotonergic function.

Regarding psychosocial factors, predisposing events such as childhood trauma, including sexual, emotional and physical abuse as well as emotional and physical neglect, have all been found to be associated with an increasing number of suicide attempts [30]. In particular, sexual and physical abuse in childhood has been shown to be strongly and independently associated with repeated suicidal behaviour [46]. Other life events that have been found to increase the risk of suicide are: the loss of a parent or a spouse and interpersonal problems [7, 17].

A number of studies have suggested that adverse life events, in patients with psychiatric disorders, may be connected to deviances in the stress system [19, 21, 38]. Currently the HPA axis appears to be involved in the response to early adverse life events in persons without psychiatric disorders. Elzinga et al. [14] found that adverse childhood events in healthy young males are associated with changes in HPA axis function. This is similar to Carpenter et al. [5], who found a diminished HPA axis in 23 healthy adults with maltreated childhood.

The aim of the present investigation was to look for a connection between adverse life events and biological stress markers among suicide attempters. We propose that patients with deviant stress markers

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have had more stressful life events than others, recently or during lifetime.

Subjects and methods

Subjects

The patients were originally recruited from the emergency room, the medical intensive care unit, or from a general psychiatric ward at the University Hospital of Lund, Sweden, shortly after a suicide attempt (here denoted "index"). Within a few days, they were referred to a ward specialised in suicidal behaviour and affective disorders. About 12 years later they were followed up.

Before follow-up, a recruitment letter was sent out, asking for participation. Later, a research nurse made a phone call, asked for consent, and offered an appointment for a research investigation.

Psychiatric diagnoses

At index, two independent psychiatrists, who were familiar with the Diagnostic and Statistic Manual of Mental Disorders, 3rd edn, revised (DSM-III-R) [1] usually diagnosed each patient. After the diagnostic procedure, they reached consensus on the main diagnosis. At the follow-up examination the DSM IV [2] was used for diagnostics, again by two medical doctors (Table 1).

A suicide attempt was defined as: "those situations in which a person has performed an actually or seemingly life threatening behaviour with the intent of jeopardizing his/her life or to give the appearance of such intent, but which has not resulted in death" [3].

Study population

In the original study (index), 102 patients participated (1986–1992), 50 men and 52 women, and they were all invited to the 12-year follow-up study (see Fig. 1). The follow-up study started in 1999 and lasted until 2002, and 43 individuals participated. One person, however, never turned up. The mean age of the participants at index was 37.7 ± 12.3 years; for the men 36.7 ± 10.8 years, and for the women 39.0 ± 13.6 years.

Deceased During the time from start of the study until the follow-up, 5 patients died a natural death, 1 uncertain suicide, and 11 patients committed suicide. Among the latter, five were men with a mean age of 41.2 ± 18.5 years, and six were women with a mean age of 41.8 ± 17.7 at index.

Follow-up Forty-two persons from the index population participated in the follow-up (21 men and 21 women) and their mean age at index was 38.2 ± 9.9 years.

Table 1 Patients participating at index and at follow-up

Principal diagnosis at index	Original study (n = 102)	Follow-up (n = 43)
Major depressive disorder (MDD)	n = 29	n = 14
Dysthymia	n = 18	n = 9
Substance use disorder	n = 8	n = 4
Adjustment disorder	n = 22	n = 9
Anxiety disorder	n = 4	–
Depressive disorder NOS	n = 12	n = 3
Psychotic disorder	n = 6	n = 2
Other diagnoses	n = 3	n = 2

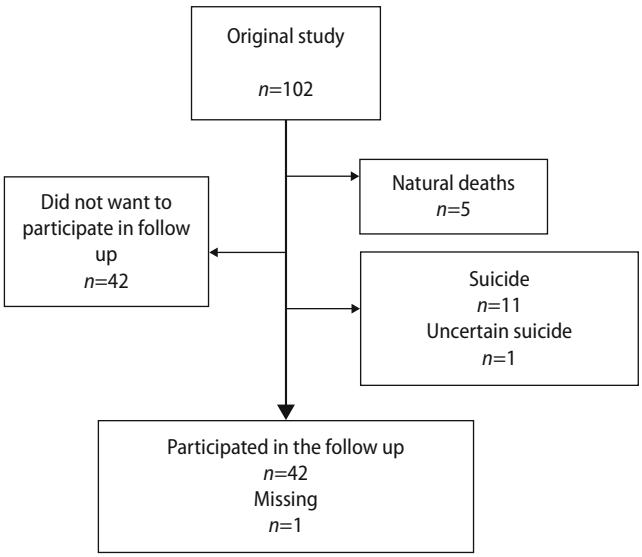

Fig. 1 The subjects in the original study (index), the suicides, the ones who did not participate, and the ones who participated in the follow up

Drop-outs Forty-two persons refrained from participating in the follow-up. The reasons for not participating were the following: 6 did not respond, 14 did not give any reasons and had just left a message on the telephone answering machine, or by letter, 8 felt well and did not want to talk about the past, 4 had problems with a somatic illness, and 2 did not feel well and were afraid to become worse. Four persons had moved, three abroad and one to the north of Sweden, and one was on a long journey abroad. One person felt insulted by psychiatric care and therefore did not want to participate, and one was not given permission from a significant other. One person gave "not enough time" as a reason. These patients had the following group characteristics at index: men (n = 22), mean age 35.0 ± 10.8 years, women (n = 20), mean age 34.6 ± 11.4 years. The main diagnoses at the time of index, according to the DSM-III-R, were: major depression (n = 10), dysthymia (n = 7), depression NOS (n = 8), adjustment disorder (n = 9), anxiety disorder (n = 3) psychotic syndrome (n = 4) and other (n = 1).

Biochemical markers

Biochemical markers in those belonging to the index study, where samples were retrieved for analyses of biochemical markers, the 3-methoxy-4hydroxyphenylglycole (MHPG) in lumbar cerebrospinal fluid (CSF), 24 h U samples (average value of 3 days) of cortisol and noradrenaline/adrenaline (NA/A), and those who participated in the follow-up examination (Table 2).

Table 2 Biochemical markers from original study and available in follow-up

	CSF-MHPG	24 h urine NA/A (average values from 3 days)	24 h urine cortisol (average values from 3 days)
Index			
Valid (n)	98	80	76
Missing (n)	4	22	26
Available at follow-up			
Valid (n)	41	35	32
Missing (n)	2	8	11

n number of patients

Table 3 Treatment after original study (index) until the 12-year follow-up study

Outpatient contacts		Inpatient treatment	Psychotropic treatment		Somatic pharmacological treatment	Treatment outcome		
Ongoing	Finished		Ongoing	Finished		Good	Unsatisfactory	Missing
n = 18	*n* = 24	*n* = 21	*n* = 18	*n* = 13	*n* = 11	*n* = 33	*n* = 7	*n* = 2

n number of patients

Sampling for biochemical analyses

At the time of the suicide attempt (index), and *before* treatment, lumbar punctures were performed and CSF samples were drawn, as described by Engström et al. [15] and 24 h urine was collected during three consecutive days.

Analyses of biochemical markers

3-Methoxy-4-hydroxyphenylglycole was analysed according to mass fragmentographic methods according to Swahn et al. [34]. The 24 h U samples of cortisol were analysed with a standard radioimmunoassay (Orion Diagnostica Cat. No: 68548, Espoo, Finland). A total of 24 h U NA/A was analysed with an electrochemical detection method according to Eriksson et al. [16], and we used the quotient of norepinephrine and epinephrine, as it reflects catecholaminergic metabolism.

Stressful events

At the follow-up, data concerning stressful life events were collected through semi-structured interviews by a senior psychiatrist together with a resident. The interview guide included multiple choice boxes (mainly "yes" or "no") that were filled in during the interview, and with additional space for comments. The patients answered detailed questions about their life and life events during three time periods; childhood (0–12 years), adolescence (13–19 years) and adulthood before index (20 years of age—index). Each period included questions about a number of things, such as contact with medical and psychiatric services, substance abuse, school, career, living conditions, and marital as well as social relationships. The interviewers noted the patients' answers into forms, which were later compiled into a database that allowed statistical analyses of the data.

We were interested in early adverse life experiences, discussed by others, so that we could compare our results. Therefore, only a subset of variables collected during the interviews are considered in the present analyses of negative life events: separation(s), feelings of neglect, sexual abuse and interpersonal problems.

Assessment of hospitalizations and treatment

Data concerning treatment after the index suicide attempt until follow-up were collected through semi-structured interviews by a senior psychiatrist together with a resident. The patients answered questions about outpatient and inpatient treatments as well as psychopharmacological treatment and their opinion concerning treatment outcome (Tables 3, 4).

Table 4 Pharmacological treatment at follow-up

None	Antidepressants	Antipsychotics	Lithium
n = 13	*n* = 11	*n* = 4	*n* = 4

Assessment of temperament

A temperament inventory, the Karolinska scales of personality (KSP) [31–33] was routinely administered to suicide attempters at the time of index, and was readministered at the follow-up. Extreme values of the KSP dimensions measure vulnerability for different forms of psychopathology. We used the socialisation scale of the KSP, which reflects childhood experiences, school and family adjustment.

Statistics

For comparing biological stress markers between the original study and follow-up, *T* tests were used. Chi-square was used to compare life events between the groups of below and above median biological stress markers. Spearman rank correlations were used to test association between the KSP item: *socialisation* at index and at follow-up as well as CSF-MHPG and NA/A values. The statistic calculations were made by use of the Statistical package for the Social Sciences, SPSS, version 15.0.

Ethical approval

The study was carried out at the Lund Suicide Research Centre at the Department of Psychiatry of Lund University Hospital. The Lund University Medical Ethics Committee had approved the study and all participants gave written informed consent.

Results

Group comparisons

Concerning CSF-MHPG, 24 h U-NA/A and U-cortisol, there was no significant difference between patients participating at the time of index and those who participated in the follow-up as well (Figs. 2, 3, 4).

There were no significant differences between suicide victims and survivors concerning CSF-MHPG (mean 41.2 ± SD 10.4 nmol/l and mean 42.5 ± SD 9.2 nmol/l; NS), 24 h U-NA/A (mean 8.6 ± SD 4.8 nmol/l and mean 7.1 ± SD 4.3 nmol/l; NS), U-cortisol (mean 169.2 ± SD 94.7 nmol/l and mean 181.9 ± SD 101.2 nmol/l; NS).

Subgroups of patients according to below and above median values of biological markers

The CSF-MHPG, 24 h U-NA/A and 24 h U-cortisol at index were divided by median values based on all participation in the original sample, into subgroups with levels below and above median, respectively. Then we

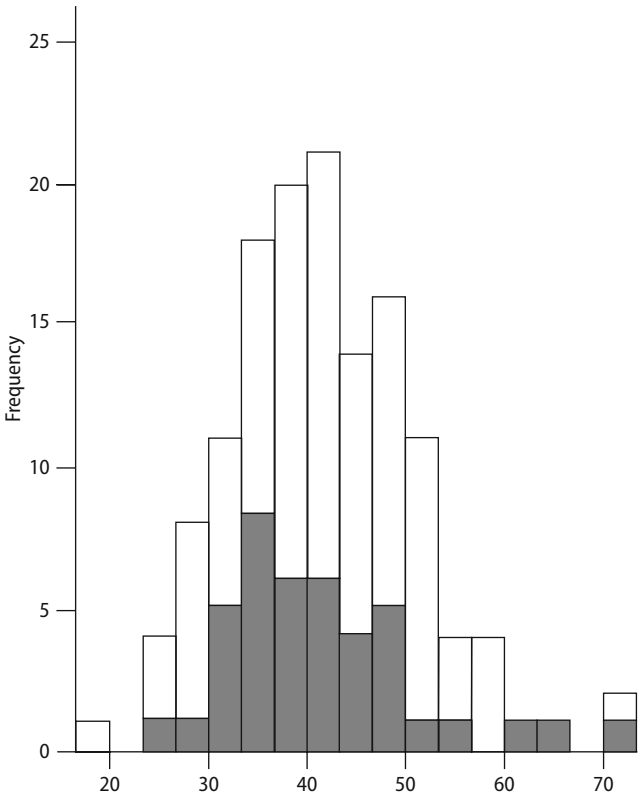

Fig. 2 CSF-MHPG. Empty boxes represent the original study ($n = 98$) and the filled boxes represent those also participating in the follow up ($n = 41$) (mean 42.5 SD ± 9.2 nmol/l and mean 41.5 SD ± 9.7 nmol/l; N.S.)

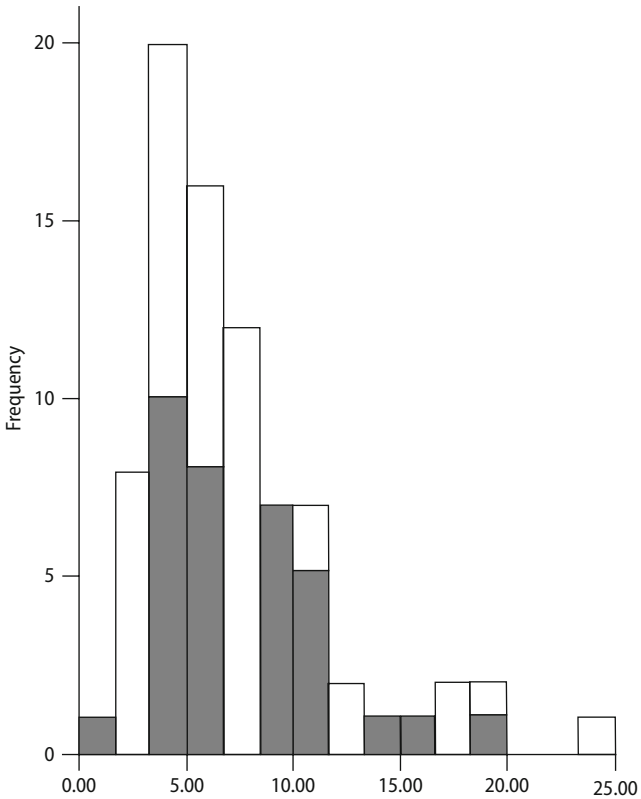

Fig. 3 U-NA/A. Empty boxes represent the original study ($n = 80$) and the filled boxes represent those also participating in the follow up ($n = 35$) (mean 7.3 SD ± 4.3 nmol/l and mean 7.3 SD ± 4.0 nmol/l; N.S.)

compared these subgroups concerning the following life events, which had occurred before the index suicide attempt in the follow-up patients: interpersonal problems, feelings of neglect, separation, and sexual abuse (Table 5).

We correlated the catecholaminergic markers CSF-MHPG and U-NA/A and, as could be expected, a significant correlation was seen (Spearman $\rho = 0.26$; $P = 0.022$).

We also correlated scores of the KSP item: *socialisation* (reflecting childhood experiences, school and family adjustment), rated at the time of the original study, with scores rated at the follow-up. A significant correlation was seen (Spearman $\rho = 0.58$; $P \leq 0.000$; Fig. 5).

Discussion

The main findings from this study can be summarised as follows. First, when average numbers of life events were compared between patients with high and low values of the catecholaminergic stress markers CSF-MHPG and 24 h U-NA/A, respectively, there were significant differences between the groups concerning experiences of sexual abuse, where those who had been afflicted had significantly higher levels of CSF-MHPG and NA/A. Second, low 24 h U-cortisol levels were associated with feelings of neglect during childhood and adolescence.

According to our calculations of stress markers, the persons who participated in the long-term follow-up study were representative for all the original 102 patients, who were studied at the time of a suicide attempt.

A definite weakness of the present study is the low number of participants and the relatively large number of dropouts. Another weakness is that the interview about life events was made at the follow-up, and not at index. However, the significant correlation between scores at index and follow-up of the KSP item *socialisation*, which reflects childhood experiences, school and family adjustment, means that the patients' views concerning predisposed events were quite similar over a long time span. A third weakness is that we only have information on CSF or urinary measures at the index suicide attempt, and not at follow-up. We, however, decided in beforehand not to collect CSF and 24 h U at the follow-up, because the patients were not expected to be medication-free at that time. In one of our previous studies, where we repeated CSF-sampling every 3 months after discharge from hospital, we e.g. found that antidepressant medication resulted in a long-term decrease of CSF MHPG [4].

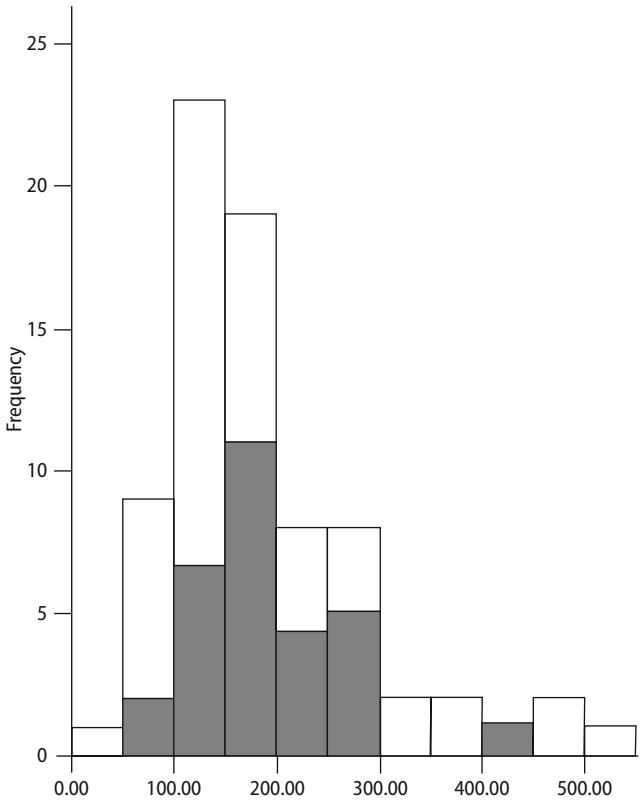

Fig. 4 U-Cortisol. Empty boxes represent the original study ($n = 76$) and the filled boxes represent those also participating in the follow up ($n = 32$) (mean 182.3 SD ± 102.2 nmol/l and mean 179.5 SD ± 78.3 nmol/l; N.S.)

The strength of the present study is thus that we were able to relate our life event findings to CSF and urinary samples, which were retrieved when the patients were supposed to be medication-free.

Our theory is that the noted stress system alterations in our suicide attempters once upon a time might have been influenced by one or more stressful events. The noted imbalance in their stress system may reflect a sensitization for experiencing new stressful situations, leading to attempted suicide. We are, however, aware of the fact that a vulnerability to adversities could depend on genetic factors as described by Caspi et al. [6].

Many studies have reported HPA overactivity in relation to suicidality in patients with various psychiatric disorders [9, 10, 20, 26, 27] but to our knowledge, little is still known about the connection with stressful life events. Van Heeringen et al. [37] compared 17 patients with a history of violent suicidal behaviour with 23 patients without a history of violent suicidal behaviour. They found evidence that HPA-axis overactivity and reduced norepinephrenic activity reflect the inability to adapt to stressful stimuli in association with violent suicidal behaviour. This behaviour was related to temperamental vulnerability and persisting difficulties in interpersonal behaviour, thus indicating that interpersonal events especially act as stressful stimuli that may precipitate suicidal behaviour.

Early adverse life experiences, such as sexual and physical abuse and feelings of neglect, might play a significant role in determining a so-called allostatic load later in life [25]. Similarly, Heim et al. [18] found that severe stress (sexual and physical abuse) early in life is associated with persistent sensitization of the HPA axis, which in turn is related to an increased risk for adulthood psychopathological conditions. These findings are consistent with results from several animal studies [8, 28]. De Bellis [12] considered feelings of neglect or reports of having been neglected during childhood and adolescence as reflecting a chronic stressor that causes anxiety- and depressive disorders during child and/or adulthood, and most likely, a dysregulation of the biological stress system. Ehnvall [13] found that patients with severe treatment-refractory affective disorders have perceived themselves as not wanted by their parents. They also had a more malignant illness course. Similar to findings in our present study, Queiroz et al. [29] found high urinary catecholamine excretion and low plasma cortisol in boys who were neglected and suffering from depression. Low U-cortisol levels have also been seen in patients with anxiety/panic disorder as well as in repeaters of suicide attempts [36, 47]. Similarly Yehuda et al. [42] showed low cortisol levels to be associated with increased risk for the development of PTSD. The same research group has in several studies

Table 5 Life events before index in subgroups according to concentrations below or above the median of CSF-MHPG, U-NA/A, U-cortisol

	CSF-MHPG median (41.00 nmol/l)		U-NA/A median (6.25 nmol/l)		U-cortisol median (160.00 nmol/l)	
	Below $n = 24$	Above $n = 17$	Below $n = 17$	Above $n = 18$	Below $n = 15$	Above $n = 17$
Life events						
Interpersonal problems	20	15	16	16	12	17
Feelings of neglect	14	13	11	12	13*	8
Separation	17	16	17	16	13	17
Sexual abuse	2	7**	1	8**	5	2

n number of patients in the follow-up
* Pearson Chi-square $P = 0.02$, ** Pearson Chi-square $P = 0.01$

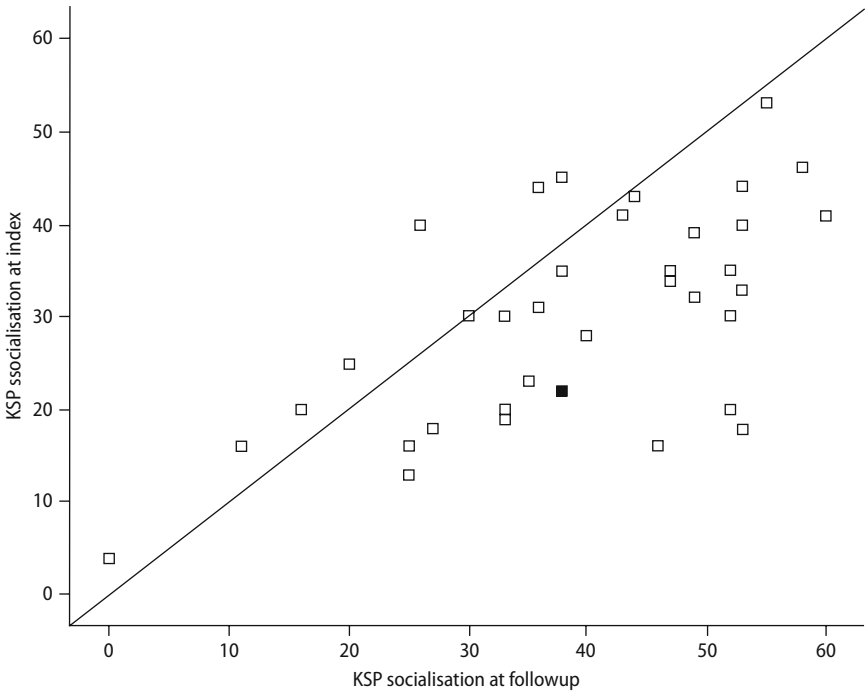

Fig. 5 The relationship between KSP socialisation scores, rated at index and at follow up, respectively ($n = 37$, ■ = 2 subjects)

[41, 43–45] investigate the relationship between neuroendocrine systems, traumatic stress and acute or chronic PTSD symptoms.

In conclusion this study has shown significant stress-system alterations in relation to some adverse life events. It seems as childhood sexual abuse and feelings of neglect are related to long-term psychobiological effects, and may also be behind depressive and/or anxiety illness during adulthood [39] reflecting an allostatic load.

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